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Case Report

A Case Report of Palmer-Planter Erythrodysesthesia Syndrome (Hand-Foot Syndrome) Due To 5-Fluorouracil in Oncology Department at Tertiary Care Hospital

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Abstract: Palmar-plantar erythrodysesthesia (PPE; hand-foot syndrome) associated with cancer chemotherapeutic agents is seen. A 40 year old female was diagnosed with stage-II cholangiocarcinoma prescribed 5-Fluorouracil (5-FU) 1gm I.V. bolus infusion. She developed redness of palms, fingers and soles associated with pain, followed by peeling of skin of fingers. Clinician diagnosed this as a case of palmer-planter dysesthesia syndrome (hand-foot syndrome) due to 5-FU. She recovered within 7 days of drug withdrawal. Palmer-planter dysesthesia syndrome (hand-foot syndrome) is particularly associated with continuous infusion of 5-FU but here it is seen with bolus infusion. Precise mechanism which leads to onset of PPE is largely unknown. The definite causal relationship is difficult to establish, as rechallenge with suspected drug was not done.
Keywords: Palmar-plantar erythrodysesthesia (PPE), 5- Fluorouracil, Hand foot syndrome

INTRODUCTION

Palmarplantar erythrodysesthesia (PPE; hand-foot syndrome) associated with chemotherapy usually presents as a tingling sensation in the palms and soles, which progresses in a few days to burning pain and well-defined swelling and erythema [1]. In severe cases there is desquamation, ulceration, blistering, and severe pain. The reaction appears to be caused by a direct toxic effect and seems to be dose-dependent, affected by both peak drug concentration and total cumulative dose. The drugs most often associated with PPE or similar syndromes are cytarabine, docetaxel , doxorubicin , and fluorouracil etc.5-Flurouracil(5-FU), an analogue of pyrimidine uracil, is an antineoplastic agent that acts as an antimetabolite by blocking the methylation of deoxyuridylic acid to thymidylic acid in DNA synthesis [2]. It is used alone or in combination with other cancer chemotherapeutic agents in the adjuvant and palliative treatment of cancer of breast, colon, esophageal, stomach, pancreas, head and neck [2]. Hand foot syndrome with 5-fluorouracil is particularly associated with continuous infusion, it has also been observed after bolus dose [1]. Here a case of palmer-planter erythrodysesthesia (Hand foot syndrome) has been reported with bolus I.V. infusion of 5-fluorouracil given in patient with stage II cholangiocarcinoma.

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CASE REPORT

A 40 year old female was diagnosed with stage-II cholangiocarcinoma (moderately differentiated adenocarcinoma) .After undergoing Whipple procedure she received adjuvant chemotherapy(1$^{s\ t}$ dose) with 5-FU 1gm I.V. infusion and Mitomycin-c 10 mg I.V. infusion on 11th January 2012 & she was called for next chemotherapy cycle on 18th January 2012. When the patient came for the 2nd dose of chemotherapy, she complained of redness of palms, fingers and soles associated with pain starts after 2 days of chemotherapy, followed by peeling of skin of fingers. There is no previous history of similar reaction. Also there is no past history of hypersensitivity reactions with any drug therapy (any type of chemical class). The clinician diagnosed this as a case of palmer-planter dysesthesia syndrome (hand-foot syndrome) due to 5-FU. The next dose of chemotherapy was stopped & changed over to Gemcitabine 1000mg/m2 on day 1 & 8 every three weekly. Tablet pyridoxine 100mg BD daily was prescribed to her. Patient gradually showed improvement and after 7 days reaction was subsided.

DISCUSSION

Palmer-planter dysesthesia syndrome (hand-foot syndrome) is particularly associated with continuous infusion but syndrome can also occur after bolus doses. Incidence in a continuous infusion therapy is 34% as compared to bolus infusion which is 13% [3]. Shari *et al.* Reports it was due to oral fluorouracil at 9th course, [4] while in this case it is due to bolus I.V. infusion at 1st course. Dose interruption is given in both cases with systemic pyridoxine.

Capecitabine is an oral fluoropyrimidine absorbed intact in the intestine and converted in the body to 5-FU, thus mimicking continuous infusion of 5-FU. PPE has been reported to be the most common adverse effect of capecitabine-containing chemotherapy, with an incidence of 45% to 68% in clinical trials [5].

Precise mechanism which lead to onset of PPE is largely unknown. Cyclooxygenase-2(cox-2) overexpression might be a potential mediator for development of PPE [3]. Fluorouracil should not be used in patient of dihydropyrimidine dehydrogenase enzyme deficiency as this can lead to increased toxicity like bonemarrow suppression, GI toxicity[1] while Janush M et.al study states that there are more chances of hand foot mouth syndrome in patient having raised level of dihydropyrimidine dehydrogenase enzyme [3]. Shari A. et.al study states that it is unknown in patient treating with inhibitor of this enzyme [4].

Plasma concentrations of fluorouracil during continuous intravenous infusion are reported to undergo circadian variations of as much as 50% of the mean, peak concentrations occurring in the middle of the night. The variation may be due to a circadian variation in the activity of the enzyme dihydropyrimidine dehydrogenase in blood, but striking interpatient variations in peak concentrations of fluorouracil and peak enzyme activity suggest that any adjustment of infusion times would need to be individualised. It has been suggested that pharmacokinetic monitoring should be investigated as a means of individualising fluorouracil doses with the aim of improving efficacy and reducing toxicity [1].

In treatment schedules with an expected rate of PPE, it is important that patient are able to recognize early symptom in order to start therapy or treatment modification without delay. Dose reduction/interruption is necessary after first episode of PPE, once the symptoms have abated therapy can usually be restarted according to original scheme [3]. Systemic strategies include pyridoxine 50 to150mg /day [1]. COX-2 inhibition has also been effective as a systemic approach for prophylaxis of chemotherapy associated PPE. Local therapy includes high potency corticosteroid and a wet-disinfectant. Nicotine patch is an interesting approach [3]. Vaso-constrictive nicotine patches are used prophylactically, 1hour before to 1hour after 5-FU infusion.

According to WHO-UMC causality categories the association of 5-flurouracil as a causal drug of hand-foot disease is “probably/likely”, as there is no rechallenge, because the drug is stopped by the physician [6]. Using the Naranjo ADR probability score, it was concluded that there was a probable association with 5-flurouracil [7]. By modified schumock and thornton criteria for preventability of an ADR, It is probably preventable [8]. By ADR severity assessment scale, it is moderately severe (lavel-3) [9].

CONCLUSION

We are reporting this case to increase awareness among prescribers about this uncommon side effect of a very common chemotherapeutic agent in the Indian scenario. Timely intervention makes this case less severe and easily curable.

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